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Risk of drug interactions and prescription appropriateness in elderly patients

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Abstract

Background: In Europe, adverse drug reactions and drug interactions are cause of considerable morbidity and mortality. In over 75s, hospital access due to adverse drug reactions can be as high as 1 in every 3.

Aims: To assess the quality of the prescribed polytherapies in the territory, in terms of the risk of drug interactions and of prescription appropriateness, in over 75s.

Methods: Randomly selected patients, over 75s, were analysed among the patients of 3 general practitioners. Their data were analysed with the INTERCheck® software. This software provided the list of drug interactions deriving from the chronic therapies. The program also provided the Beers criteria and the STOPP criteria related to the drugs, highlighting potentially inappropriate drugs.

Results: 188 patients were included in the study. 216 serious or very serious drug interactions have been identified. 92 patients (48.9%) were at risk of at least one serious or very serious interaction. The cut-off of the correlation between the number of drugs taken and the risk of incurring a serious or very serious interaction was found to be 5 (AUC = 0.833, sensitivity = 87%, $p < 0.001$). Patients on >= 4 drugs were at risk of prescriptive inappropriateness with a sensitivity of 84% (AUC = 0.781, $p < 0.0001$).

Conclusions: Focusing on patients with at least 4 drugs in therapy is the right strategy to reduce the risks associated with polypharmacy.

Keywords: acetylsalicylic acid; benzodiazepines; escitalopram; furosemide; PPI; sertraline

Introduction

Europe's population is getting old. At 1 January 2016, for example in Italy, individuals aged 65 and over represented 22.3% of the total population; those aged 80 and over were 6.8% of the total, while those over 90 years old were 1.2% of the total. The average life span for men has reached 80.6 years, for women 85.1 years [1]. The total population in Europe is projected to increase from 511 million in 2016 to 520 million in 2070. However, the working-age population (people aged between 15 and 64) will decrease significantly from 333 million in 2016 to 292 million in 2070. These projected changes in the population structure reflect assumptions on fertility rates, life expectancy and migration flows. The old-age dependency ratio (people aged 65 and above relative to those aged 15 to 64) in the Europe is projected to increase by 21.6 percentage points, from 29.6% in 2016 to 51.2% in 2070 [2].

"Older patients" in medicine is usually associated with "comorbidity" and "polypharmacy".

Adverse drug reaction (ADR) is defined as “an unpleasant or dangerous reaction, resulting from the use of a pharmaceutical product, which suggests a risk from future administration and determines the need for specific treatment, dosage modification or withdrawal of the drug from the market" [3]. The overall number of ADRs is often underestimated as reporting is often on a voluntary basis: 94% of missed reports can be reached [4]. In Europe, adverse drug reactions are the cause of considerable morbidity and mortality. It is estimated that approximately 5% of hospital admissions are due to ADRs, and that they cause around 197,000 deaths a year at European level. For patients over the age of 75, hospital admission due to an ADR may even be 1 in every 3 [5, 6].

DDI (Drug-drug interactions) represent another problem of the elderly patient. The comorbidities and the increase in the average age generate poly-therapies with high risk of DDI. Drug interactions can compromise the patient's health and cause hospitalization [7].

A recent survey conducted in Denmark has shown that general practitioners are often left alone in the management of polypharmacy set up in hospitals [8]. Also in our study, it emerged that it is unfortunately common that the specialist prescribes following the guidelines without considering the patient's age, the comorbidities and the risks associated with polypharmacy.

The Beers criteria are the most commonly used to support physicians in preventing ADRs in the elderly [9].

The STOPP criteria (screening tool of older persons) are potentially associated with avoidable adverse drug events capable of causing urgent hospitalization in the elderly [10].

The aim of the study was to assess the quality of the prescribed polypharmacy in the territory, in terms of the risk of drug interactions and of prescription appropriateness, in the elderly patient over 75 years of age.

Methods

Data were collected from the databases of three general practitioners from the city of Turin, Italy.

Mario Negri Research Institute in Milan has developed an informatic support system called INTERCheck® to help the clinician in the prevention of DDIs and ADRs. The software provides a list of the potential DDIs associated with the patient's pharmacological therapies, classifying them according to clinical relevance in four categories:

A. (Minor): interaction not relevant from the clinical point of view

B. (Moderate): interaction associated with an uncertain or variable event

C. (Major): interaction associated with a serious event; it can be managed (e.g. by adjusting the dose).

D. (Contraindicated or Very Severe): interaction associated with a serious event; co-administration should be avoided or careful monitoring established.

INTERCheck® has also been validated for clinical practice confirming its effectiveness in reducing severe potential DDIs [11]. The program also provides the Beers criteria and the STOPP criteria related to the drugs present in the chronic therapy of the patient, highlighting the potentially inappropriate drugs and advised against the drugs to be used with caution.

For the purposes of this study, only class C and D interactions were considered. A database was then filled with the patients' personal data, the drugs taken, the interactions emerged, the severity of these interactions, the drugs inappropriately prescribed.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

Statistics

For the analysis of quantitative variables, the Kruskal-Wallis test was used, for the dichotomous qualitative variables, the Fisher test was used. The correlation between quantitative variables was performed with Pearson test. The ability of the number of the drugs in therapy to predict potential DDIs or inappropriate prescriptions was evaluated using receiver operating characteristic (ROC) curve analysis.

A p value of less than 0.05 was considered significant. The statistical analysis was performed with MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

188 patients randomly selected among patients with an age greater than or equal to 75 years were selected for the study. Table 1 shows the data regarding the sex and age of the patients enrolled. 53.2% (100) of the patients were male, 46.8% (88) were females. The age ranged from 75 to 96 years and the median was 83.5 years. The largest group of patients was the the younger one (75-79).

Table 1.

The number of drugs taken ranged from 0 to 17, with an average of 6.5 drugs per patient. In patients older than 84 years, the mean use of drugs per patients was 7.3, in patients younger than 85 years the mean use of drugs per patients was 5.9 (p =

0.04). There was no significant difference between the female and male population as regards the number of drugs taken (6.5 in both sexes, p = 0.74).

A total of 190 different drugs were prescribed. In the supplementary table 1 the most frequently used drugs are reported; the most common one was hydrochlorothiazide followed by acetylsalicylic acid and furosemide.

Considering the pharmacological class of the drugs, diuretics were the most prescribed, followed by ß-blockers, proton pump inhibitors and benzodiazepines (supplementary table 2)**.**

Overall, pharmacological interactions, classified as serious or very serious, identified by the INTERCheck® software, were 216. 92 patients (48.9% of the total) presented the risk of at least one serious or very serious interaction. Forty-sixth of these patients were at risk for a class D (very serious) interaction. **Fig.1** shows the number of patients presenting an increasing number of serious or very serious risk interactions. The most recurrent cases are those with one or two risk interactions, but there were patients with up to 6 interactions.

Fig.1

An older age was not correlated to the risk of presenting at least one serious or very serious interaction (p = 0.14); the same applied to sex (p = 0.84).

Instead, a statistically significant correlation emerged between the number of drugs taken and the risk of incurring into a serious or very serious interaction: the cut-off for the predictability was 5 (AUC = 0.833, sensitivity = 86.9%, P < 0.001) (**Fig.2**).

Fig.2

The prescribed drugs involved in serious or very serious interactions were 82 out of a total of 190: in the supplementary table 3 the complete list is reported.

The first 4 drugs responsible for class C or D interactions were: furosemide, acetylsalicylic acid, escitalopram and sertraline. Specific interactions of these drugs are reported in supplementary table 4, supplementary table 5, supplementary table 6, supplementary table 7. Noteworthy, these four drugs alone are responsible for 86 interactions out of a total of 216. The most frequent interaction was between furosemide and digoxin (10 patients, 5.3% of patients). Classifying the drugs into categories, the selective serotonin reuptake inhibitors (SSRI) / serotonin and norepinephrine reuptake inhibitors (SNRI) family was the main culprit of potentially dangerous drug interactions: in the supplementary table 8 the interactions of this pharmacological class are reported. 28% of all interactions identified were related to this pharmacological category and almost half (46%) of all interactions were due to SSRIs / SNRIs, furosemide and acetylsalicylic acid (Fig.3).

Fig.3

The list of the drugs found to be inappropriate according to the Beers and STOPP criteria is reported in the supplementary table 9.

In particular, the drugs belonging to the benzodiazepine family were found to be inappropriate in 100% of the 56 prescriptions identified in the study patient population. Bromazepam and lorazepam were the two most commonly prescribed molecules. Patient's sex was not associated with the probability of a benzodiazepine prescription ($p = 0.79$).

Considering proton pump inhibitors (PPI) (supplementary table 10), 42% of prescriptions were found to be inappropriate. The classes of benzodiazepines, PPI and non-steroidal anti-inflammatory drugs (NSAID) alone represented 69% of all inappropriate prescriptions identified (Fig.4).

Fig.4

The predictive ability of the number of drugs on the risk of presenting a potentially inappropriate drug in the therapy was then analysed: having at least 4 drugs in therapy predicts this risk with a sensitivity of 84%, AUC = 0.781, $p < 0.0001$) (Fig.5).

Fig.5

Discussion

The study population was balanced for the sex of the participants, as well as for the over-75 age groups included.

It is remarkable that till to 17 drugs were prescribed to a single patient. A mean of 6.5 drugs per patient resulted in our study. This is a significant result because this values is associated in literature with a greater risk of inappropriate prescriptions, DDI and ADR [12, 13]. Belonging to the older age group (age > 85 years) was associated with the risk of polytherapy. No statistically significant differences were found between the male and female population. It emerged that the most commonly prescribed drugs were hydrochlorothiazide, acetylsalicylic acid and furosemide. Following these three drugs we found cholecalciferol, bisoprolol and amlodipine, the last two respectively a ß-blocker and a calcium channel blocker used in arterial hypertension therapies. It is therefore evident that the drugs used in the treatment of cardiovascular diseases play a preponderant role in composing the poly-therapies of our older patients. This data confirms what emerged from a study conducted in Italy in 2009 [14]: even in this case the most prescribed drugs were those to protect the cardiovascular system. Classifying the drugs according to pharmacological categories other interesting data emerged. Specifically, a diuretic was found to be prescribed in more than half of the patients, followed by ß-blockers, PPIs, benzodiazepines, angiotensin-converting enzyme (ACE)-inhibitors and SSRIs. Even PPIs and psychiatric drugs play a significant role in the poly-therapies of our elderly, a role that will be analysed later.

It is very significant that almost half of the patients presented the real risk of a DDI classifiable as serious or very serious. It's probably due to the lack of attention at the present time to this problem by health personnel; our patients take a real risk

when subjected to complex therapies for equally complex diseases. Our data show that there was no correlation between the risk of presenting a serious or very serious interaction and age; similar assessment can be made for sex. In contrast, other studies found a correlation between the risk of severe interactions and age [14, 15]. This probably derives from the fact that we have included only over-75s patients, while in the 2 studies mentioned also patients over-60-65s have been included. Instead, an important correlation was found between the number of drugs taken and the risk of dangerous DDI. Specifically, the cut-off of 5 drugs allows us to predict with a sensitivity of 87% the risk of presenting at least one potentially serious DDI. This data confirms what is already present in the few studies in the literature in this regard [14, 16]. This data is fundamental because it would make it possible to rationalize the work of the general practitioner, who could in this way focus the evaluation, using INTERCheck® software, in patients with at least 5 drugs in continuous therapy, in order to reduce the workload and to identify potentially dangerous DDI with acceptable sensitivity. The drugs responsible for these DDIs, in order of frequency, were furosemide, followed by acetylsalicylic acid, escitalopram and sertraline: on their own these four drugs were responsible for 86 interactions out of a total of 216 identified. Grouping the drugs by pharmacological classes showed that 28%, almost a third, of all the identified DDIs were due to a drug belonging to the SSRI / SNRI class. Adding acetylsalicylic acid and furosemide leads to almost half of all identified DDIs. The conclusion is drawn that it would be sufficient for the general practitioner to pay attention to the use of three categories of drugs to avoid almost half of all DDIs of serious or very serious risk class. When a potential risk interaction is identified, the choice can be the de-prescription when possible; alternatively, the monitoring (often hematochemical or electrocardiographic).

The study revealed 166 inappropriate prescriptions according to the Beers and STOPP criteria, out of a total of 1220 prescribed drugs (13.6%). The most frequently inappropriate drug was found to be bromazepam, followed by acetylsalicylic acid, lorazepam and pantoprazole.

According to the Beers criteria “the elderly have an increased sensitivity to benzodiazepines and the metabolism of those with a long duration of action is slower”. In general, in the elderly all benzodiazepines increase the risk of impairment of cognitive abilities, delirium, falls, fractures and road accidents. Those with long half-lives (such as diazepam, flurazepam, flunitrazepam or, clonazepam) may be appropriate in the following conditions: seizures, rapid eye movements in sleep disorders, withdrawal from benzodiazepines or ethanol, severe generalized anxiety disorder, periprocedural anaesthesia.". The drugs of this class are often prescribed to elderly patients for disorders related to sleep and anxiety by the general practitioner, sometimes by the hospital doctor during hospitalization. The de-prescription of these drugs is extremely difficult, but it is the right path to take. A systematic review in 2008 showed how the de-prescription of benzodiazepines in

the elderly reduces the number of falls, improves cognitive abilities and psychomotor functioning [17]. The solution to this problem should be at the origin: a greater knowledge on the problems connected to sleep and on the clinical and pharmacological way to face them, and a greater attention to the anamnesis and to the first prescription of these molecules, especially in elderly patients.

Regarding PPIs, according to the Beers criteria "It should be avoided the use for more than 8 weeks except in the following conditions: subjects at high risk (oral therapy with corticosteroids or chronic use of NSAIDs), erosive esophagitis, Barrett's oesophagus, pathological hypersecretion or demonstrated need for maintenance therapy (failure of suspension or ineffectiveness of anti-H2). Rationale for inappropriateness: increases the risk of Clostridium difficile infections, bone loss and fractures.". Our results confirmed that of previous studies, like an observational, longitudinal, retrospective and descriptive study in an internal medicine ward in a Portuguese hospital, in which polypharmacy was present in more than 70% of admitted patients and PPI were the most common inappropriate prescription at discharge (17.2%) [18]. As to the expenses for this overuse/abuse of PPI prescription, it has been shown that PPIs are overprescribed worldwide in both primary and hospital care, so that 25%–70% of patients taking these drugs have no appropriate indications and it has been calculated that almost 2 billion pounds are being spent unnecessarily on PPIs each year [19]. It is therefore evident that the prescription of this category of drugs must always pass from a careful evaluation of the risk / benefit ratio, especially in the elderly patient.

The study showed a statistically significant correlation between the number of drugs present in the patient's ongoing therapy and the risk that at least one of the prescriptions in therapy was inappropriate. Using the cut-off of 4 drugs this risk was predicted with a sensitivity of 84% and a specificity of 58%. This data suggests that it could be a good strategy for the general practitioner to focus on patients who have more than 4 drugs in therapy, in order to optimize time and resources. Furthermore, only 3 pharmacological classes accounted for 69% of all the inappropriate prescriptions: this is fundamental. After benzodiazepines, PPIs and NSAID were most at risk for inappropriate prescription. In the elderly patient it may be sufficient to focus on these three categories, further facilitating the difficult task of de-prescribing.

Some weaknesses of this study must be emphasized. Since the study was carried out in a relatively small area, its results are not necessarily immediately applicable to other territorial realities, but the consistency of the results found with the data in the literature [14, 15] and the high number of analysed prescriptions (about 1200 prescriptions of 190 different drugs) contribute to giving strength to the study. With regard to the new data that this study brings, if other studies with

larger case series have analysed the theme of DDI [14], very few studies are comparable to our study in analysing prescriptive appropriateness using real data from general practitioners' databases.

In conclusion, the role of the general practitioner appears to be crucial: he's the last prescriber, so he should be the "guardian" of therapies prescribed to patients. This role will have to be confirmed over time, by educating patients to converge on the clinic of their general practitioner following each new prescription suggested by specialists, and by raising awareness among the general practitioners of a careful prescription and de-prescription.

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Compliance with ethical standards

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Mazzola P, Rimoldi SML, Rossi P, et al (2016) Aging in Italy: The Need for New Welfare Strategies in an Old Country. Gerontologist 56:383–390. https://doi.org/10.1093/geront/gnv152
2. European Commission (2018) The 2018 Ageing Report: economic and budgetary projections for the EU Member States (2016-2070)
3. Edwards IR, Aronson JK (2000) Adverse drug reactions: definitions, diagnosis, and management. Lancet 356:1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9

4. Hazell L, Shakir SAW (2006) Under-Reporting of Adverse Drug Reactions. Drug Saf 29:385–396. https://doi.org/10.2165/00002018-200629050-00003
5. Ribeiro-Vaz I, Santos CC, Cruz-Correia R (2016) Promoting adverse drug reaction reporting: comparison of different approaches. Rev Saude Publica 50:14. https://doi.org/10.1590/S1518-8787.2016050006122
6. Chan M, Nicklason F, Vial JH Adverse drug events as a cause of hospital admission in the elderly. Intern Med J 31:199–205
7. Becker ML, Kallewaard M, Caspers PWJ, et al (2007) Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. Pharmacoepidemiol Drug Saf 16:641–51. https://doi.org/10.1002/pds.1351
8. Laursen J, Kornholt J, Betzer C, et al (2018) General Practitioners' Barriers Toward Medication Reviews in Polymedicated Multimorbid Patients: How can a Focus on the Pharmacotherapy in an Outpatient Clinic Support GPs? Heal Serv Res Manag Epidemiol 5:2333392818792169. https://doi.org/10.1177/2333392818792169
9. (2015) American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 63:2227–2246. https://doi.org/10.1111/jgs.13702
10. Hamilton H, Gallagher P, Ryan C, et al (2011) Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med 171:1013–9. https://doi.org/10.1001/archinternmed.2011.215
11. Antoniazzi S, Chiarelli MT, Nobili A, et al (2015) The value of software that provides clinically relevant information on drug interactions. Eur J Intern Med 26:e52-3. https://doi.org/10.1016/j.ejim.2015.07.004
12. Mantelli S, Jungo KT, Rozsnyai Z, et al (2018) How general practitioners would deprescribe in frail oldest-old with polypharmacy — the LESS study. BMC Fam Pract 19:169. https://doi.org/10.1186/s12875-018-0856-9
13. Green JL, Hawley JN, Rask KJ (2007) Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother 5:31–9
14. Nobili A, Pasina L, Tettamanti M, et al (2009) Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J Clin Pharm Ther 34:377–86. https://doi.org/10.1111/j.1365-2710.2009.01021.x
15. Bjerrum L, Andersen M, Petersen G, Kragstrup J (2003) Exposure to potential drug interactions in primary health care. Scand J Prim Health Care 21:153–8. https://doi.org/10.1080/02813430310001806
16. Johnell K, Klarin I (2007) The relationship between number of drugs and potential drug-drug interactions in the

elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug Saf 30:911–8. https://doi.org/10.2165/00002018-200730100-00009

17. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG (2008) Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging 25:1021–31. https://doi.org/10.2165/0002512-200825120-00004.

18. Urzal J, Pedro AB, Oliveira IF, et al (2019) Inappropriate Prescribing to Elderly Patients in an Internal Medicine Ward. Acta Med Port 32:141–148. https://doi.org/10.20344/amp.10683

19. Forgacs I, Loganayagam A (2008) Overprescribing proton pump inhibitors. BMJ 336:2–3. https://doi.org/10.1136/bmj.39406.449456.BE

Table 1. Sex and age classes

	Sex		Total
Age classes	F	M	
75-79	24	36	60 (31.9%)
80-84	28	20	48 (25.5%)
85-89	24	20	44 (23.4%)
90-95	8	14	22 (11.7%)
95-99	4	10	14 (7.4%)
	88 (46.8%)	100 (53.2%)	188

Fig. 1 Number of interactions per patient

Fig. 2 Number of drugs taken and risk of serious or very serious interaction

Fig. 3 Main causes of serious or very serious drug interactions

Fig. 4 Inappropriate prescriptions

Fig. 5 ROC curve of the predictive ability of the number of drugs on the risk of presenting a potentially inappropriate drug in therapy